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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,765	08/09/2001	Michael J. Mahan	220002060723	6765

23308 7590 12/20/2004

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 12/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,765	MAHAN ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22-26 and 31-35* is/are pending in the application.

4a) Of the above claim(s) *8-13,23-26 and 31-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,14-20,22,35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-20,22-26 and 31-35* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20,22-26 and 31-35 are pending.
Claims 1, 3, 15-18 have been amended.
Claims 21, 27-30 have been canceled.
New claim 35 has been submitted.
Claims 8-13,23-26,31-34, and non-elected species of newly submitted claim 35 stand withdrawn from consideration.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 4, 2004 has been entered.

Election/Restrictions

2. Newly submitted claim 35 is directed to a number of species of invention that are independent or distinct from the invention originally examined; Claim 35 recites species of invention previously non-elected and therefore, except for the previously elected species of Salmonella, the non-elected species stand withdrawn from consideration.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 35, in so far as it recites non-elected species of invention, is herein withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Terminal Disclaimer

3. The terminal disclaimer filed on October 4, 2004 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 09/928,227 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Response to Arguments

4. Applicant's arguments with respect to claims 1-7, 15-20,22 and 35 (Salmonella) have been considered but are moot in view of the new ground(s) of rejection.

Claim Objections

5. Claims 6 and 35 are objected to because of the following informalities: Claims 6 and 35 recited non-elected inventions and therefore recite species that were not elected. Appropriate correction is required.

6. Claim 2 is objected to under 37 CFR 1.75 (c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 2 defines the bacteria to be altered in changing the bacteria genome, thus redefining the invention to not require the alteration to be in the DNA adenine methylase gene as required by Applicant's newly submitted claim amendments for claim 1. Claim 2 broadens the scope of claim 1 by not requiring the alteration to the bacterial DNA adenine methylase gene, but the alteration can be anywhere in the bacteria's genome.

7. Claim 4 is objected to under 37 CFR 1.75 (c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 4 defines the bacteria to be altered rather than the DNA adenine methylase gene being altered as set forth in newly amended claim 1. Claim 4 may be trying to add an additional alteration or does not comprise the alteration of the DNA adenine methylase gene. If the bacteria of claim 4 -------- further comprises an additional mutation-------, then this introductory phrase should be used to amend claim 4.

8. Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 5 indirectly depends from amended claim 1 and defines the heterologous nucleotide, which alters DNA adenine methylase gene to be in a plasmid, while claim 1 defines the DNA adenine methylase to be in the bacterial "gene"; Claim 5 broadens the

scope of claims 4 and 1 by redefining where the alteration of the DNA adenine methylase gene activity is located. Amended Claim 1 defines the alteration to be in the native bacterial DNA adenine methylase gene, while claim 5 defines that alteration to be a heterologous nucleotide inserted into a plasmid. Claim 5 is not further limiting of claims 4 and 1 from which it depends, as the claimed genus of bacteria is not so claimed that the native *dam* gene is only found on a plasmid rather than bacterial chromosome gene.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 2 recites the limitation "genome " and depends from claim 1 which recites the term "gene"; the term "gene" does not provide antecedent basis for a complete bacterial genome. Claim 1 does not provide antecedent basis for the term "genome" in the recitation of the term "gene". There is insufficient antecedent basis for the term "genome" in claim 1.

11. Claim 3 recites the limitations "a native sequence", but this phrase lacks antecedent basis in claim 1. There is insufficient antecedent basis for this limitation in claim 1 that requires the change to be in the bacterial DNA adenine methylase gene and not in any "native sequence" as set forth in claim 3. The phrase "a native sequence" is not required to be the native sequence of the DNA adenine methylase gene of the bacteria of claim 1. The phrase "a native sequence" is defined by the indefinite article "a", which does not require the mutation/alteration to be in the DNA adenine methylase gene of claim 1, but can be in any native sequence that can directly or indirectly effect the DNA adenine methylase gene. Claim 3 is broader in scope than claim 1

through changing where the alteration is located, as well as setting forth claim limitations that lack antecedent basis in independent claim 1.

12. Claim 4 recites the phrase "the bacteria are altered by a heterologous nucleotide"; this phrase lacks antecedent basis in claim 1 which recites the phrase "bacteria with an altered DNA adenine methylase gene". What is altered in claim 1 is a gene, and not the entire bacteria. The change in claim 1 is not at any location but in the gene of the bacteria's DNA adenine methylase gene. The term "DNA adenine methylase gene" in claim 1 defines a location for the alteration, and does not provide antecedent basis for the location of the alteration being the entire bacteria as recited in claim 4.

13. Claim 5 recites the limitation "a plasmid" in defining where the insertion of the heteroloogus nucleotide is operatively placed. There is insufficient antecedent basis for the term "plasmid"in the claim 1. The altered DNA adenine methylase gene is not defined to be in a plasmid in the bacteria of claim 1. The bacteria's DNA adenine methylase gene would be chromosomally associated and would not be a heterologous nucleotide sequence inserted in a plasmid. Claim 5 sets forth the term "plasmid" which lacks antecedent basis in claim 1 from which it depends as the alteration has been defined by Applicant's amendment to be in the bacterial DNA adenine methylase gene, and not due to the presence of a heterologous coding sequence inserted into a plasmid which expresses DNA adenine methylase protein activity. The alteration of claim 1 is in the native gene, and not due to the presence of a heterologous DNA adenine methylase coding sequence.

14. Claim 16 seeks to define the protein "Dam activity" to be altered by a heterologo9us nucleotide, and depends from claim 15 which no longer recites the protein activity, but recites

gene activity. The recitation of protein activity in claim 16 lacks antecedent basis in claim 15 , wherein claim 15 has been amended to define the activity of the gene and altered gene activity. The term recited in claim 15 is "dam" and not "Dam"; utilization of a capital "Dam" is indicative of the protein encoded by the gene. Claim 16 should be amended to refer to the gene activity recited in claim 15.

15. Claim 17 also depends from claim 15 and recites the phrase "Dam activity", which lacks antecedent basis in amended claim 15 which is now directed to gene activity, rather than protein activity. Amendment of claim 17 should be directed to altered gene activity to obviate this rejection.

16. Claim 18 has been amended to define the mutation to include "a heterologous nucleotide containing a sequence corresponding to a Dam gene". The term "corresponding to" in claim 18 is a relative term which renders the claim indefinite. The term "corresponding to" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. How or where does the heterologous nucleotide corresponds to the "mutation in the regulatory or coding regions of the DNA adenine methylase (Dam) gene" is not distinctly claimed. How the heterologous nucleotide introduces a type of mutation that corresponds to the already existing dam gene in the bacterial strain is not clearly defined in the claim. Does this combination of claim limitations intend the mutation to be outside the regulatory or coding regions of the gene? The corresponding nucleotide is not clearly nor distinctly claimed.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

18. Claims 1-7, 15-17, 18-20,22,35 are rejected under 35 U.S.C. 102(b) as being anticipated by Torreblanca et al (1996).

(Instant claims 1-7, 15-17) The attenuated strains of Salmonella typhimurium were combined with a pharmaceutically acceptable carrier. Carriers disclosed include NCE liquid medium containing 0.2% glucose (see page 16, col. 2, paragraph 4) or E medium without glucose (see page 18, col. 1, paragraph 3).

(Instant claims 18-20) Torreblanca et al disclose compositions of mutant strains of Salmonella typhimurium (see abstract, first full sentence and Table 1, page 17) which are lacking DNA adenine methylase gene activity through insertion and deletion mutations. Salmonella mutant strains that lacked or over produced DNA adenine methylase were produced (see page 20, col. 2, paragraph 3) through insertion, deletion or addition of a heterologous nucleotide sequence (see page 24, col. 1, paragraphs 2-3). The insertions were accomplished through the introduction of a mutation into a regulatory sequence for dam (see page 24, col. 1, paragraphs 2-4 and Table 1).

While the mutant strains were viable (see page 24, col. 1, paragraph 4 and col. 2, paragraphs 1-3) , attenuated characteristics were evidenced in these strains. The mutant Salmonella strains are attenuated due to increased spontaneous mutations, moderate SOS induction, enhancement of duplication segregation, inviability of dam recA and dam recB mutants and suppression of inviabilty of the dam recA and dam recB combination by mutations that eliminate mismatch repair.

(Instant claims 4, 22, 35) Mutant Salmonella strains with altered native dam genes were also additionally altered with a heterologous nucleotide through the insertion of an E.coli dam+ gene carried on a plasmid (see page 20, col. 2, paragraphs 2).

The reference anticipates the instantly claimed invention.

19. Claims 1-4,6-7, 15-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Brawer et al (May 1998).

Brawer et al disclose the instantly claimed invention directed to an immunogenic composition comprising an acceptable carrier (LB broth, see Figure 2,) together with a *dam* gene mutant strain of Salmonella D220, wherein the activity of the mutant strains was altered relative to the wild-type strain (see page 530, col. 1, abstract, truncated Dam protein), wherein the mutant strain comprised a heterologous nucleotide (TN10dTet insertion).

Brawer et al also produced dam mutant strains through a deletion in the dam gene using pDeltadam-804 (see page 532, col. 2, paragraph 3; page 533, col. 1, paragraph 1). The reference anticipates the instantly claimed invention.

20. Claims 1-4, 6-7,14-17,18-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Kleanthous et al (US Pat. 6,585,975, priority date April 30, 1998) as evidenced by Torreblanca et al (1996).

(Instant claims 1-3, 15-17,18-20) Kleanthous et al disclose a composition having reduced bacterial virulence, specifically an attenuated pathogenic Salmonella. Altered Dam activity is obtained through the *dam* gene being inactivated either chemically or genetically (see col. 2, lines 51-67 and col. 3, lines 1-7, especially col. 2, lines 6-7 "genetic mutagenesis" col. 3, lines 13-19 "deletions, inversions, insertions and substitutions") utilizing methods known in the art (see col. 2, lines 51-52, as evidenced by Torreblanca et al (1996)).

(Instant claim 4) Salmonella typhimurium attenuated mutants express a heterologous antigen (see col. 1, line 59-60, col. 3, lines 13-19; col. 3, lines 60-64; see col. 3, lines 6-7 and evidence provided by Torreblanca et al , 1996)) encoded by a *Helicobacter pylori, H.felis, H. mustelae,* and *H.heilmanii* heterologous nucleotide sequence (see col. 1, lines 11-30, col. 4, lines 1-35) that is operatively inserted into a first plasmid (see col. 4, lines 3-10; see mutants inactivated (see col. 2, lines 51-60; especially line 58 "genes).

(Instant claims 6-7) Salmonella vectors disclosed include S. typhi, typhimurium, enteritidis, Dublin, Minnesota and choleraesuis.

(Instant claim 14) The attenuated pathogenic Salmonella is formulated into a composition that comprises a pharmaceutically acceptable carrier (see at least col. 6-7) together with an adjuvant (see col. 5, line 19).

The reference inherently anticipates the instantly claimed invention.

Conclusion

21. This is a non-final action.

22. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Manovich et al (1989); Hafner et al (1991); Heithoff, DM et al (1999);Ritchie (1986 and 1988); Palmer et al (1994) are cited to show *dam* gene mutant strains of bacteria.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
December 13, 2004

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